AF/1614/6

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SUBSTITUTE for PTO/SB/17(05-03)"FEE TRANSMITTAL for FY 2003"

FEE TRANSMITTAL

Patent fees are subject to annual revision.

TOTAL AMOUNT OF PAYMENT $320

Complete if Known	
Application Number	10/010,678
Filing Date	December 7, 2001
First Named Inventor	G.J. Gormley et al.
Examiner Name	V.Y. Kim
Group Art Unit	1614
Attorney Docket Number	19109DE

METHOD OF PAYMENT (Check one)

☒ Deposit Account

Deposit Account Number: 13-2755

Deposit Account Name: Merck & Co., Inc.

The Director is authorized to:

☒ Charge fee(s) indicated below ☒ Credit any overpayments

☒ Charge any additional fee(s) during the pendency of this application

FEE CALCULATION

1. BASIC FILING FEE

Large Fee Code	Entity Fee ($)	Fee Description	Fee Paid
1001	750	Utility filing fee	
1002	330	Design filing fee	
1004	750	Reissue filing fee	
1005	160	Provisional filing fee	

SUBTOTAL(1) $0

2. EXTRA CLAIM FEES

			Extra		Fee from below	Fee Paid
Total Claims		- 20 ** =	0	x	$18 =	0
Independent Claims		- 3 ** =	0	x	$84 =	0
Multiple Dependent Claims					$280 =	

***or number previously paid, if greater; For Reissues, see below*

Large Fee Code	Entity Fee ($)	Fee Description
1202	18	Claims in excess of 20
1201	84	Independent claims in excess of 3
1203	280	Multiple dependent claim, if not paid
1204	84	**Reissue independent claims over original patent
1205	18	**Reissue claims in excess of 20 and over original patent

SUBTOTAL(2) $0

FEE CALCULATION (continued)

3. ADDITIONAL FEES

Fee Code	Large Entity Fee ($)	Fee Description	Fee Paid
1051	130	Surcharge - late filing fee or oath	
1812	2,520	For filing a request for *ex parte* reexamination	
1251	110	Extension for reply within first month	
1252	410	Extension for reply within second month	
1253	930	Extension for reply within third month	
1254	1,450	Extension for reply within fourth month	
1255	1,970	Extension for reply within fifth month	
1401	320	Notice of Appeal	
1402	320	Filing a brief in support of an appeal	320
1403	280	Request for oral hearing	
1452	110	Petition to revive - unavoidable	
1453	1,300	Petition to revive - unintentional	
1501	1,300	Utility issue fee (or reissue)	
1502	470	Design issue fee	
1460	130	Petitions to the Commissioner	
1807	50	Processing fee under 37 CFR 1.17(q)	
1806	180	Submission of Information Disclosure Statement	
8021	40	Recording each patent assignment per property (times number of properties)	
1809	750	Filing a submission after final rejection (37 CFR 1.129(a))	
1810	750	For each additional invention to be examined (37 CFR 1.129(b))	
1801	750	Request for Continued Examination (RCE)	
Other fee (specify)			
Other fee (specify)			

SUBTOTAL(3) $320

SUBMITTED BY

Typed or Printed Name	CATHERINE D. FITCH			Reg. Number	36,502
Signature	Catherine D. Fitch	Date	06/24/2003	Deposit Account User ID	

IN DUPLICATE

Application Number: 10/010,678

Filing Date: 12/07/2001

First Named Inventor: G.J. Gormley et al.

Group Art Unit: 1614

Examiner Name: V.Y. Kim

Attorney Docket Number: 19109DE

FIRST CLASS MAIL CERTIFICATE

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MERCK & CO., INC.

MAILED BY _____ DATE 6/24/2003

PATENT

#11
10/3
JRI

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	G.J. Gormley et al.		
Serial No.:	10/010,678	Case No.: 19109DE	Art Unit: 1614
Filed:	December 7, 2001		Examiner: V. Y. Kim
For:	TRANSDERMAL TREATMENT WITH 5-ALPHA-REDUCTASE INHIBITORS		

Mail Stop Appeal Brief- Patents
Commissioner for Patents
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Alexandria, VA 22313-1450

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MERCK & CO., INC.
By _____ Date 6/24/2003

APPEAL UNDER 37 C.F.R. 1.192

Sir:

The present Brief is submitted in triplicate under the provisions of 37 C.F.R. 1.192 in support of an appeal from the January 30, 2003, rejection of Claims 28 to 37. The Notice of Appeal was timely filed on April 25, 2003. Appellants hereby respectfully seek to have the rejections of Claims 28-37 overturned.

REAL PARTY IN INTEREST

The real party in interest is Merck & Co., Inc. of Rahway, New Jersey, by assignment recorded at the U.S. Patent and Trademark Office on April 26, 1996 (Reel 7916/Frame 0548). The inventors of the present application assigned their interests to Merck & Co., Inc., in an assignment executed on April 25, 1994.

RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to the Appellants, or known to Appellants' legal representative, that will directly affect the Board's decision in the pending appeal.

STATUS OF CLAIMS

Claims pending: 28-37.
Claims cancelled: none.
Claims allowed: none.
Claims rejected: 28-37.
Claims on appeal: 28-37.

A complete copy of the Claims on appeal is provided in the accompanying Appendix.

STATUS OF AMENDMENTS

One preliminary amendment and two amendments were filed for this application. A preliminary amendment was filed on December 7, 2001, accompanying a new divisional application under 37 CFR 1.53(b) based on parent Application Serial No. 09/699,906. A second amendment under 37 CFR § 1.111 was filed on October 16, 2002. The two amendments were entered by the Examiner. The list of claims presented in Appendix I reflects entry of these amendments. A third amendment under 37 CFR § 1.116 was filed on April 25, 2003 (after Final Office Action) but was not entered by the Examiner allegedly because it raised new issues that would require further consideration and/or search.

SUMMARY OF THE INVENTION

The present invention defined in Claims 28-32 under appeal relates to a method of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor. The invention defined in Claims 33-35 under appeal relates to a method of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a

therapeutically effective amount of 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one. The invention defined in Claims 36-37 under appeal relates to a transdermal skin patch comprising a therapeutically effective amount of a 5 alpha-reductase 2 inhibitor. A copy of the claims appears in Appendix I.

ISSUES

There are two issues being presented for review by the Board of Appeals. The first issue on appeal is rejection of Claims 28-29 and 31-34 under 35 U.S.C. §102(b) as being anticipated by Rasmusson et al. (EP 0285382 A2). The second issue on appeal is the rejection of Claims 30, and 35-37 under 35 U.S.C. §103(a) as being unpatentable over Rasmusson et al. (EP 0285382 A2) in view of Goldman (US 5,407,944). Appellants believe both rejections to be erroneous, as will be explained in the Argument Section below.

GROUPING OF CLAIMS

For the purpose of this Appeal, the Claims shall be grouped as follows:

Group I: Claims 28-29 and 31-34
Group II: Claims 30 and 35
Group III: Claims 36-37

The Claims of Groups I-III are considered to be separately patentable and do not stand or fall together. The Claims of Group I are directed to methods of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one. The Claims of Group II are limited to methods of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, wherein the 5alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, is transdermally administered by a transdermal skin patch. The Claims of Group III are directed to transdermal skin patches comprising a therapeutically effective amount of a 5 alpha-reductase 2 inhibitor.

ARGUMENT

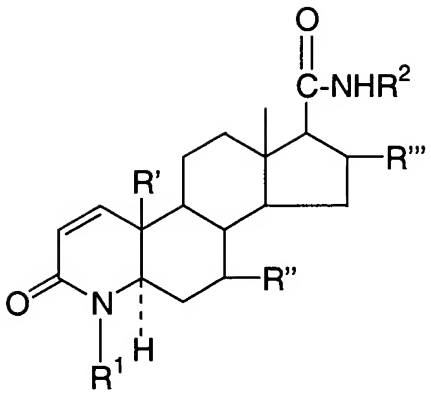
As set forth in detail below, Appellants submit that the methods of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor and the methods of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a therapeutically effective amount of 17β-(N-*tert*-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one are not anticipated by the cited reference. In addition, the transdermal skin patch comprising a therapeutically effective amount of a 5 alpha-reductase 2 inhibitor is nonobvious and patentably distinct over the cited references. Applicants submit that the Board of Appeals should reverse the Examiner's rejections of Claims 28-37. Favorable action by the Board is respectfully requested.

Issue 1: Claims 28-29 and 31-34 are anticipated by Rasmusson et al. (EP 0285382 A2) under 35 U.S.C. §102(b).

The Examiner's Rationale

Claims 28-29 and 31-34 were rejected under 35 U.S.C. §102(b) as being anticipated by Rasmusson et al. (EP 0285382 A2). On pages 4-5 of Office Action dated July 16, 2002, (Paper No. 4), the Examiner stated:

> Rasmusson teaches a treatment of androgenic alopecia using 5 alpha reductase inhibitors (e.g., 17-beta-N-monosubstituted-carbamoyl-4-aza-5alpha-androst-1-ene-3-ones). Rasmusson also teaches the limitations cited in claims 29 and 34 (i.e. a treatment of male pattern baldness) and the species required by claim 33 (i.e. 17-β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one) as a preferred species, see abstract; page 2, line 47; examples 6-12 and claims 1-4 and 6-8. It also teaches the patented compounds having the formula found in patented claim 1 as follows:



I

(wherein:
R^1 is hydrogen, methyl or ethyl;
R^2 is a branched chain alkyl of 3-12 carbon atoms;
R' is hydrogen or methyl;
R" is hydrogen or β-methyl;
R''' is hydrogen, α-methyl or β-methyl) for the manufacture of a medicament useful for treating androgenic alopecia.

The formulas I and II required by the instant claims 31 and 32 are encompassed by the patented formula shown above (supra). [...] All the critical elements required by the instant claims are taught by the cited reference. Thus, all the claimed subject matter is rejected over the prior art of the record.

In the Final Office Action dated January 30, 2003 (Paper No. 7, pages 2-3), the Examiner essentially reiterated her position with respect to the rejection of Claims 28-29 and 31-34 under 35 U.S.C. §102(b) adding, however, that 5 alpha reductase inhibitors taught by Rasmusson are in the form of cream, lotion or ointment. ("Rasmusson teaches a treatment of androgenic alopecia using 5 alpha reductase inhibitors (e.g., 17-beta-N-monosubstituted-carbamoyl-4-aza-5alpha-androst-1-ene-3-ones) *such as in the form of cream, lotion or ointment*, see examples and claims." (emphasis added) Page 2, Final Office Action dated January 30, 2003 (Paper No. 7)).

The Examiner maintained her rejection of Claims 28-29 and 31-34 stating on page 5 of the Final Office Action:

[...] the term "transdermal" includes any application that is applied though the unbroken skin (refers to medications applied directly to the skin (creams, ointments, patch, etc), see dictionary, World net 1.7 or Webster [...]. Topical compositions (i.e. cream, lotion, ointment) taught by the Rasmusson encompass the critical element required by the instant claims (i.e. transdermal

application). Thus, claims 28-29 and 31-34 are anticipated by the Rasmusson reference and the rejection is maintained.

I. The 35 U.S.C. § 102 (b) Novelty Rejection of Claims 28-29 and 31-34 is Improper

Claims 28-29 and 31-34 under appeal teach methods of treating androgenic alopecia comprising *transdermally administering* to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor and methods of treating androgenic alopecia comprising *transdermally administering* to a person in need of such treatment a therapeutically effective amount of 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one. As used in Claims 28-29 and 31-34, the verbal phrase "transdermally administering" constitutes a claim limitation because it states the intended method of administration of 5alpha-reductase 2 inhibitors. (See, e.g., Practicing Law Institute, Landis On Mechanics of Patent Claim Drafting, 2000, §37.)

Appellants submit that in making the rejection of Claims 28-29 and 31-34 under 35 U.S.C. § 102(b) the Examiner failed to show that Claims 28-29 and 31-34 are anticipated. "A claim is anticipated only if each and every element [(limitation)] as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Appellants submit that in making the rejection of Claims 28-29 and 31-34 under 35 U.S.C. § 102 (b) the Examiner improperly interpreted the "transdermally administering" claim limitation as being encompassed within topical compositions (cream, lotion or ointment) recited by the Rasmusson reference. Appellants submit that transdermal ("through-the-skin") administration constitutes a separate and distinct claim limitation from a topical ("cutaneous") administration of 5alpha-reductase 2 inhibitors. Appellants' assertion is based primarily on intrinsic evidence (Appellants' original patent specification) and is also fully supported by extrinsic evidence (Technical Treatises and Dictionaries). See Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1583 (Fed. Cir. 1996) ("[T]he intrinsic evidence of record, *i.e.,* the patent itself, including the claims, the specification and, if in evidence, the prosecution history" "is the most significant source of the legally operative meaning of

disputed claim language" and that "[i]n most situations, an analysis of the intrinsic evidence alone will resolve any ambiguity in a disputed claim term.")

Starting in paragraph 3 on page 6 (i.e., page 6, line 28) of the original patent specification, Appellants teach transdermal administration of 5alpha-reductase 2 inhibitors:

> "The compounds of the present invention may be administered [...] via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in the art. To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen."

Topical administration of 5alpha-reductase 2 inhibitors is taught in a separate paragraph of the original patent specification (page 6, paragraph 2, i.e., page 6, lines 17-27):

> "For the treatment of adrogenic alopecia including male pattern boldness, acne vulgaris, seborrhea, and female hirsutism, the 5α-reductase 2 inhibitor compounds may be administered in a combination with a pharmaceutically acceptable carrier adapted for topical administration. Topical pharmaceutical compositions may be, e.g., in the form of a solution, cream, ointment, gel, lotion, shampoo or aerosol formulation adapted for application to the skin. Topical pharmaceutical compositions useful in the method of treatment of the present invention may include about 0.001% to 0.1% of the active compound in admixture with the pharmaceutically acceptable carrier."

Appellants submit that the fact that Appellants teach transdermal administration and topical administration in two different paragraphs suggests that the two routes of administration are in fact not interchangeable. Specifically, while Appellants' original patent disclosure associates topical administration with "solution[s], cream[s], ointment[s], gel[s], lotion[s], shampoo[s] or aerosol formulation[s]" (original patent application, page 6, lines 22-24), transdermal administration is linked to the use of transdermal skin patches only (original patent application, page 6, lines 32-34). This distinction is critical for understanding the difference between a topical and a transdermal administration. While solutions, creams, ointments, etc. are generally applied *intermittently* as a single daily dose or two, three, or four, etc. daily doses, a transdermal administration is *continuous* throughout the dosage regimen. ("To be administered in the form of a transdermal delivery system, the dosage administration will, of course, be continuous rather than intermittent throughout the dosage regimen." Original patent application, Page 7, lines 1-2).

Furthermore, Applicants submit that a skilled artisan would recognize that the difference between a topical and a transdermal administration also lies therein that in a topical (cutaneous) route of administration drugs applied to the skin are generally used for their local effects, while in a transdermal route of administration drugs are generally delivered systemically (bodywide). (See e.g., The Merck Manual, Second Home Edition, Chapter 11, Drug Administration and Kinetics, Thomas N. Tozer, Ph.D., Drug Administration; Appendix I; "Some drugs are delivered bodywide through a patch on the skin. [...] Through a patch, the drug can be delivered more slowly and continuously for many hours or days or longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particularly useful for drugs that are quickly eliminated from the body, because such drugs, if taken in other forms, would have to be taken frequently.") In fact, Rasmusson et al. themselves distinguish between topical and systemic administration by contraposing the two separate routes of administration within a sentence: "The present invention is thus also concerned with providing suitable *topical and systemic* pharmaceutical formulations for use in the novel methods of treatment of the present invention" (emphasis added, EP 0285382 A2, Page 6, lines 7-8.) However, while Rasmusson et al. disclose such topical formulations as solutions, creams or gels, they do not teach using transdermal patches (for systemic delivery of 5alpha-reductase 2 inhibitors).

Because Rasmusson does not teach a transdermal use of 5alpha-reductase 2 inhibitors it also does not anticipate Claims 28-29 and 31-34 under appeal. (See, e.g., Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 1053 (Fed. Cir. 1987) "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.") Appellants respectfully request that the novelty rejection of Claims 28-29 and 31-34 under 35 U.S.C. § 102 (b) be reversed.

Issue 2: Claims 30 and 35-37 are rejected under 35 U.S.C. §103(a) as being unpatentable over Rasmusson et al. (EP 0285382 A2) in view of Goldman (US 5,407,944).

The Examiner's Rationale

Claims 30 and 35-37 were rejected by the Examiner under 35 U.S.C. § 103(a) as being unpatentable over Rasmusson et al. (EP 0285382 A2) in view of Goldman (US 5,407,944). On pages 6-7 of Office Action dated July 16, 2002 (Paper No. 4), the Examiner stated:

> Rasmusson et al's teaching is mentioned in 102 rejection. For instance, the patented claim 8 teaches various alternative topical formulations including solution, cream, ointment, gel, shampoo or aerosol. Rasmusson teaches most elements required by the instant claims 30 and 35-37 except a topical application being formulated in the form of a transdermal skin patch.
>
> However, it would be obvious to one of ordinary skill in the art to make a transdermal skin patch comprising a 5α-reductase 2 inhibitor to treat androgenic alopecia (e.g. male pattern baldness) when Rasmusson's reference is modified with Goldman because Goldman suggests that a pharmaceutical preparation could be made in the form of a topical transdermal skin patch comprising a composition containing 5α-reductase 2 inhibitor (e.g. finasteride®), see column 6, lines 10 and 20, especially line 28 [sic]. Goldman teaches a method for promoting hair growth using a vasodilator in combination with estradiol and/or a 5α-reductase 2 inhibitor. Since the techniques for formulating a transdermal patch is [sic] well within the skilled level of the artisan having an ordinary skill in the art, one would have had the reasonable expectation of success for treating androgenic alopecia by utilizing a skin patch formulation of 5α-reductase 2 inhibitor as an active component taught by Rasmusson. Thus one would have been motivated to modify Rasmusson's teaching to include a transdermal skin patch to extent the applicability and acceptance by the patient who prefers a patch application to fit their needs, wherein the increased compliance would enhance the therapeutic efficacy and achieve cost-effective treatment via short duration of therapy and because this is seen as an alternative means to deliver medications. It is noted that finasteride® [sic] is 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one.
>
> One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same (or similar) ingredients and share common utilities, and pertinent to the problem which applicant is concerning. MPEP 2141.01(a)

In the Final Office Action dated January 30, 2003 (Paper No. 7, pages 4-5), the Examiner reiterated her position with respect to the rejection of Claims 30 and 35-37 under 35 U.S.C. § 103(a). In response to Appellants' arguments, the Examiner also stated:

> The Examiner would not agree on applicant's argument [that the skin patch containing 5alpha-reductase inhibitor is not specifically taught by Goldman (US 5407944)] because the patented claims 17 and 19 which are directed to the combination of vasodilator and 5-alpha reductase inhibitor in topical preparation that could be formulated in skin patch in light of the patented disclosure (column 6, lines 10-20). Thus it would have been obvious to one of ordinary skill in the art at the time of the invention made to modify Rasmusson's teaching with Goldman's to make skin patch composition to increase the selection option and [sic] the improve the quality of the therapy by enhancing the compliance wherein the extended formulation would benefit the patient and fit the patient's need.

II. The § 103 (a) Obviousness Rejection of Claims 30 and 35 is Improper

Claims 30 and 35 under appeal teach methods of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, wherein the 5alpha-reductase 2 inhibitor, including 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one, is transdermally administered by a transdermal skin patch. As used in Claims 30 and 35, the verbal phrase "transdermally administering" constitutes a claim limitation because it states the intended method of administration of 5alpha-reductase 2 inhibitors. Also, the adjective "transdermal" in "transdermal skin patch" constitutes a claim limitation of Claims 30 and 35 because it states the intended method of use of the skin patch. (See, e.g., Practising Law Institute, Landis On Mechanics of Patent Claim Drafting, 2000, §37.)

Appellants submit that in making the rejection of Claims 30 and 35 under 35 U.S.C. § 103 the Examiner failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Third, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Appellants submit that neither Rasmusson nor Gold, separately or in combination, teach or suggest all the claim limitations of Claims 30 and 35. Specifically, neither Rasmusson nor Gold, separately or in combination, teach or suggest a *transdermal* skin patch comprising a 5alpha-reductase type 2 inhibitor, including finasteride. Also, neither Rasmusson nor Gold, separately or in combination, teach or suggest a *transdermally* administering a 5alpha-reductase type 2 inhibitor, including finasteride. Rasmusson discloses 5alpha-reductase type 2 inhibitors but does not teach or suggest any transdermal patches or administering 5alpha-reductase type 2 inhibitors transdermally. Goldman recites certain commercially-available formulations (some of which are in the form of transdermal patches) namely:

(1) Minoxidil as a topical solution (col. 3, lines 39-52);
(2) Minoxidil in a tablet form (col 3., lines 53-62);
(3) Nitroglycerin as a transdermal system (col. 4 lines 1-6)
(4) Diazoxide as a capsule or suspension (col 4 lines 7-18)
(5) Nifedipine as a capsule (col. 4, lines 19-38);
(6) Nifedipine as a controlled release tablet for oral administration (col. 4 lines 42-56)
(7) 17beta-estradiol as tablet or cream (col. 4, line 57 to col. 5 line 28);
(8) 17beta-estradiol as a transdermal patch (col. 5, lines 29-42);
(9) Finasteride as a tablet (col. 5, lines 43-62).

However, Goldman does not teach a transdermal skin patch comprising a composition containing 5alpha-reductase type 2 inhibitor, including finasteride. Nor does Goldman teach administering a 5alpha-reductase type 2 inhibitor, including finasteride, transdermally. Of the nine formulations recited by Goldman, only finasteride is a 5alpha-reductase inhibitor. Minoxidil, nitroglycerine, diazoxide, and nifedipine are vasodilators under the definition of the Goldman patent, and 17-beta-estradiol is an estradiol. Therefore read in context of the particular formulations cited above, Goldman teaches away from and discourages Appellants to try a transdermal skin patch containing 5alpha-reductase type 2 inhibitors and/or a transdermal administration of 5alpha-reductase type 2 inhibitors, because Goldman exemplifies vasodilators and estradiols as transdermal patches but discloses 5alpha-reductase inhibitors in the form of a tablet only (col. 5, lines 43-62). Appellants submit that it is improper to combine references for the purpose of making a 35 U.S.C. § 103 rejection

where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)

Appellants submit that in making the rejection of Claims 30 and 35 under 35 U.S.C. § 103 the Examiner improperly interpreted both the "*transdermal* patch" claim limitation and the "*transdermally* administering" claim limitation as being encompassed within topical compositions recited by Goldman. Appellants submit that transdermal ("through-the-skin") administration constitutes a separate and distinct claim limitation from a topical ("cutaneous") administration of 5alpha-reductase 2 inhibitors. The difference between a topical and a transdermal administration lies, *inter alia*, therein that in a topical (cutaneous) route of administration drugs applied to the skin are generally used for their local effects, while in a transdermal route of administration drugs are generally delivered systemically (bodywide). Similarly, a transdermal patch is generally used to deliver drugs systemically (bodywide) rather than locally. (See e.g., The Merck Manual, Second Home Edition, Chapter 11, Drug Administration and Kinetics, Thomas N. Tozer, Ph.D., Drug Administration; Appendix I; "Some drugs are delivered bodywide through a patch on the skin. [...] Through a patch, the drug can be delivered more slowly and continuously for many hours or days or longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particularly useful for drugs that are quickly eliminated from the body, because such drugs, if taken in other forms, would have to be taken frequently.")

The Examiner's failure to appreciate this difference is best illustrated by the following assertions made by the Examiner: (1) "Goldman suggests that a pharmaceutical preparation could be made in the form of a *topical transdermal skin patch* comprising a composition containing 5α-reductase 2 inhibitor", and (2) "[t]he Examiner would not agree on applicant's argument because the patented claims 17 and 19 which are directed to the combination of vasodilator and 5-alpha reductase inhibitor in *topical preparation that could be formulated in skin patch* in light of the patented disclosure" (column 6, lines 10-20) (emphasis added). Some of the Examiner's confusion appears to arise because the word "topical" has at least two meanings: (1) that the formulation is applied to the skin and (2) that the formulation has a local effect. While the Examiner seems to be making her rejections based on the first meaning of the word, Appellants make the topical-transdermal distinction in their disclosure based on the second. While shampoos, gels, creams, etc. fit both definitions in that they are applied to the skin and exhibit a local effect, transdermal

skin patches invented by the Appellants for administration of 5alpha-reductase 2 inhibitors are attached to the skin as well, but their effect is generally systemic. Thus, while relying on the wrong definition of the word "topical" in making her rejections the Examiner clearly failed to appreciate the true spirit of the Appellants invention.

In addition, the mere fact that the prior art could be modified to result in the claimed invention does not make the modification obvious unless the prior art suggests the desirability of the modification. *See In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). A determination of obviousness cannot be based on what a skilled person might try or find obvious to try. The Federal Circuit in *In re Tomlinson*, 150 U.S.P.Q. 623 (C.C.P.A. 1966) noted that permitting patentability determinations based on an "obvious to try" test "would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of 'research.'" While it may have been "obvious to try" to administer 5alpha-reductase 2 inhibitor transdermally using a transdermal skin patch, neither Rasmusson nor Goldman, separately or in combination, suggest the desirability of a transdermal administration using a transdermal skin patch comprising 5alpha-reductase 2 inhibitors. Thus a person of ordinary skill in the art would have lacked the motivation to combine the teachings of Rasmusson and Goldman to arrive at the Appellants' invention. Given the teachings of Rasmusson and Goldman, the practitioner with ordinary skill in the art would also not have reasonably expected that a 5alpha-reductase inhibitor could be administered transdermally. Hence, the claimed method of treatment is a non-obvious solution to the problem addressed by the Applicant in the present invention.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of the invention as recited in Claims 30 and 35 because the references cited by the Examiner do not teach all the claim limitations and because the Examiner failed to successfully show a suggestion or motivation to combine the reference teachings and a reasonable expectation of success. Accordingly, it is requested that the Board of Patent Appeals and Interferences overturn the Examiner's finding of obviousness and allow Claims 30 and 35.

III. The § 103 (a) Obviousness Rejection of Claims 36-37 is Improper

Claims 36-37 under appeal teach a *transdermal* skin patch comprising a therapeutically effective amount of a 5 alpha-reductase 2 inhibitor. As used in Claims 36-37, the adjective "transdermal" constitutes a claim limitation because it states the intended method of use of a skin patch. (See, e.g., Practising Law Institute, Landis On Mechanics of Patent Claim Drafting, 2000, §37.)

Appellants submit that in making the rejection of Claims 36-37 under 35 U.S.C. § 103 the Examiner failed to establish a *prima facie* case of obviousness. To establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Third, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Appellants submit that neither Rasmusson nor Gold, separately or in combination, teach or suggest all the claim limitations of Claims 36-37. Specifically, neither Rasmusson nor Gold, separately or in combination, teach or suggest a *transdermal* skin patch comprising a 5alpha-reductase type 2 inhibitor, including finasteride. Rasmusson discloses 5alpha-reductase type 2 inhibitors but does not teach or suggest any transdermal patches. Goldman recites certain commercially-available formulations (some of which are in the form of transdermal patches) namely:

(10) Minoxidil as a topical solution (col. 3, lines 39-52);
(11) Minoxidil in a tablet form (col 3., lines 53-62);
(12) Nitroglycerin as a transdermal system (col. 4,lines 1-6)
(13) Diazoxide as a capsule or suspension (col 4,lines 7-18)
(14) Nifedipine as a capsule (col. 4, lines 19-38);
(15) Nifedipine as a controlled release tablet for oral administration (col. 4 lines 42-56)
(16) 17beta-estradiol as tablet or cream (col. 4, line 57 to col. 5 line 28);
(17) 17beta-estradiol as a transdermal patch (col. 5, lines 29-42);
(18) Finasteride as a tablet (col. 5, lines 43-62).

However, Goldman does not teach a transdermal skin patch comprising a composition containing 5alpha-reductase type 2 inhibitor, including finasteride. Of the nine formulations recited by Goldman, only finasteride is a 5alpha-reductase inhibitor. Minoxidil, nitroglycerine, diazoxide, and nifedipine are vasodilators under the definition of the Goldman patent, and 17-beta-estradiol is an estradiol. Therefore read in context of the particular formulations cited above, Goldman teaches away from and discourages Appellants to try a transdermal skin patch containing 5alpha-reductase type 2 inhibitors, because Goldman exemplifies vasodilators and estradiols as transdermal patches but discloses 5alpha-reductase inhibitors in the form of a tablet only (col. 5, lines 43-62). Appellants submit that it is improper to combine references for the purpose of making a 35 U.S.C. § 103 rejection where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)

Appellants submit that in making the rejection of Claims 36-37 under 35 U.S.C. § 103 the Examiner improperly interpreted the "*transdermal* patch" claim limitation as being encompassed within topical compositions recited by Goldman. Appellants submit that transdermal ("through-the-skin") administration constitutes a separate and distinct claim limitation from a topical ("cutaneous") administration of 5alpha-reductase 2 inhibitors. The difference between a topical and a transdermal administration lies, *inter alia*, therein that in a topical (cutaneous) route of administration drugs applied to the skin are generally used for their local effects, while in a transdermal route of administration drugs are generally delivered systemically (bodywide). (See e.g., The Merck Manual, Second Home Edition, Chapter 11, Drug Administration and Kinetics, Thomas N. Tozer, Ph.D., Drug Administration; Appendix I; "Some drugs are delivered bodywide through a patch on the skin. [...] Through a patch, the drug can be delivered more slowly and continuously for many hours or days or longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particularly useful for drugs that are quickly eliminated from the body, because such drugs, if taken in other forms, would have to be taken frequently.")

The Examiner's failure to appreciate this difference is best illustrated by the following assertions made by the Examiner: (1) "Goldman suggests that a pharmaceutical preparation could be made in the form of a *topical transdermal skin patch* comprising a composition containing 5α-reductase 2 inhibitor", and (2) "[t]he Examiner would not agree on applicant's argument because the patented claims 17 and 19 which are directed to the

combination of vasodilator and 5-alpha reductase inhibitor in *topical preparation that could be formulated in skin patch* in light of the patented disclosure" (column 6, lines 10-20) (emphasis added). Some of the Examiner's confusion appears to arise because the word "topical" has at least two meanings: (1) that the formulation is applied to the skin and (2) that the formulation has a local effect. While the Examiner seems to be making her rejections based on the first meaning of the word, Appellants make the topical-transdermal distinction in their disclosure based on the second. While shampoos, gels, creams, etc. fit both definitions in that they are applied to the skin and exhibit a local effect, transdermal skin patches invented by the Appellants for administration of 5alpha-reductase 2 inhibitors are attached to the skin as well, but their effect is generally systemic. Thus, while relying on the wrong definition of the word "topical" in making her rejections the Examiner clearly failed to appreciate the true spirit of the Appellants invention.

In addition, the mere fact that the prior art could be modified to result in the claimed invention does not make the modification obvious unless the prior art suggests the desirability of the modification. *See In re Gordon*, 221 U.S.P.Q. 1125 (Fed. Cir. 1984). A determination of obviousness cannot be based on what a skilled person might try or find obvious to try. The Federal Circuit in *In re Tomlinson*, 150 U.S.P.Q. 623 (C.C.P.A. 1966) noted that permitting patentability determinations based on an "obvious to try" test "would not only be contrary to statute but result in a marked deterioration of the entire patent system as an incentive to invest in those efforts and attempts which go by the name of 'research.'" While it may have been "obvious to try" to administer 5alpha-reductase 2 inhibitor in a skin patch, neither Rasmusson nor Goldman, separately or in combination, suggest the desirability of a transdermal skin patch comprising 5alpha-reductase 2 inhibitors. Thus a person of ordinary skill in the art would have lacked the motivation to combine the teachings of Rasmusson and Goldman to arrive at the Appellants' invention. Given the teachings of Rasmusson and Goldman, the practitioner with ordinary skill in the art would also not have reasonably expected that a 5alpha-reductase inhibitor could be administered transdermally. Hence, the claimed method of treatment is a non-obvious solution to the problem addressed by the Applicant in the present invention.

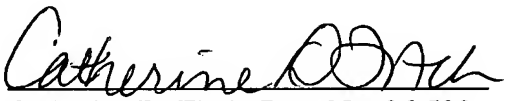
Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness of the invention as recited in Claims 36-37 because the references cited by the Examiner do not teach all the claim limitations and because the Examiner failed to

successfully show a suggestion or motivation to combine the reference teachings and a reasonable expectation of success. Accordingly, it is requested that the Board of Patent Appeals and Interferences overturn the Examiner's finding of obviousness and allow Claims 36-37.

SUMMARY

For the foregoing reasons, Appellants maintain that the references of record do not anticipate the invention as claimed in Claims 28-29 and 31-34, and do not render obvious the invention as claimed in Claims 30 and 35-37 in the subject application. The Board of Patent Appeals and Interferences is respectfully requested to overturn the Examiner's rejections and to allow Claims 28-37.

Respectfully submitted,

By 

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Date: June 24, 2003
Submitted in triplicate

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APPENDIX I

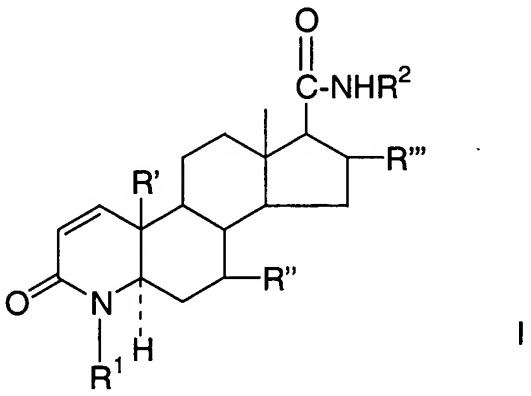
The claims on appeal are as follows:

28. A method of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a therapeutically effective amount of a 5alpha-reductase 2 inhibitor.

29. The method according to Claim 28, wherein androgenic alopecia is male pattern baldness.

30. The method according to Claim 28, wherein the 5alpha-reductase 2 inhibitor is transdermally administered by a transdermal skin patch.

31. The method according to Claim 28, wherein the 5alpha-reductase 2 inhibitor has the structural formula I:

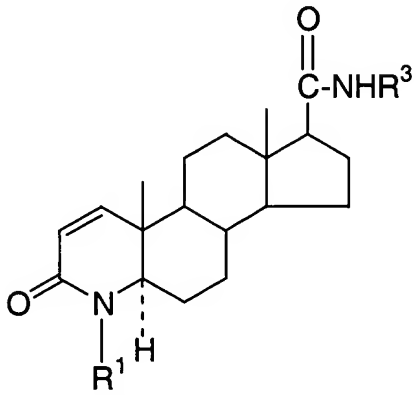


I

or a pharmaceutically acceptable salt thereof wherein:
R^1 is hydrogen, methyl or ethyl;
R^2 is a hydrocarbon radical selected from straight and branched chain alkyl of from 1-12 carbons or monocyclic aryl optionally containing 1 or more lower alkyl substituents of from 1-2 carbon atoms and/or 1 or more halogen substituents selected from Cl, F, and Br;
R' is hydrogen or methyl;
R" is hydrogen or β-methyl; and

R''' is hydrogen, α-methyl or β-methyl.

32. The method according to Claim 28, wherein the 5alpha-reductase 2 inhibitor has the structural formula II:



II

or a pharmaceutically acceptable salt thereof, wherein:
R^1 is hydrogen or methyl; and
R^3 is branched chain alkyl of from 4 to 8 carbons.

33. A method of treating androgenic alopecia comprising transdermally administering to a person in need of such treatment a therapeutically effective amount of 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one.

34. The method of Claim 33 wherein androgenic alopecia is male pattern baldness.

35. The method according to Claim 33, wherein the 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one inhibitor is transdermally administered by a transdermal skin patch.

36. A transdermal skin patch comprising a therapeutically effective amount of a 5 alpha-reductase 2 inhibitor.

37. The transdermal skin patch according to Claim 36 wherein the 5alpha-reductase 2 inhibitor is 17β-(N-tert-butylcarbamoyl)-4-aza-5α-androst-1-ene-3-one.

APPENDIX II

Drug Administration

Contributor: Thomas N. Tozer, PhD

Drugs are introduced into the body by several routes. They may be taken by mouth (orally); given by injection into a vein (intravenously), into a muscle (intramuscularly), into the space around the spinal cord (intrathecally), or beneath the skin (subcutaneously); placed under the tongue (sublingually); inserted in the rectum (rectally) or vagina (vaginally); instilled in the eye (by the ocular route); sprayed into the nose and absorbed through the nasal membranes (nasally); breathed into the lungs, usually through the mouth (by inhalation); applied to the skin (cutaneously) for a local (topical) or bodywide (systemic) effect; or delivered through the skin by a patch (transdermally) for a systemic effect. Each route has specific purposes, advantages, and disadvantages.

Oral Route: Because the oral route is the most convenient and usually the safest and least expensive, it is the one most often used. However, it has limitations because of the way a drug typically moves through the digestive tract. For drugs administered orally, absorption may begin in the mouth and stomach, but usually, most of the drug is absorbed from the small intestine. The drug passes through the intestinal wall and then the liver before it is transported via the bloodstream to its target site. The intestinal wall and liver chemically alter (metabolize) many drugs, decreasing the amount reaching the bloodstream. Consequently, for the same effect, such drugs are often given in smaller doses when they are injected directly into the bloodstream (intravenously).

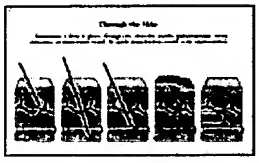
When a drug is taken orally, food and other drugs in the digestive tract may affect how much of and how fast the drug is absorbed. Thus, some drugs should be taken on an empty stomach, others should be taken with food, others should not be taken with certain other drugs, and still others cannot be taken orally at all.

Some orally administered drugs irritate the digestive tract; for example, aspirin and most other nonsteroidal anti-inflammatory drugs can harm the lining of the stomach and small intestine and can cause or aggravate preexisting ulcers. Other drugs are absorbed poorly or erratically in the digestive tract or are destroyed by the acid and digestive enzymes in the stomach.

Other routes are usually used only when the oral route cannot be used: for example, when a person cannot take anything by mouth, when a drug must be administered rapidly or in a precise or very high dose, or when a drug is poorly or erratically absorbed from the

digestive tract.

Injection Routes: Administration by injection (parenteral administration) includes the subcutaneous, intramuscular, intravenous, and intrathecal routes. A drug product can be prepared or manufactured in ways that prolong drug absorption from the injection site for hours, days, or longer; such products do not need to be administered as often as drug products with more rapid absorption.



See the figure Through the Skin.

For the subcutaneous route, a needle is inserted into fatty tissue just beneath the skin. The drug is injected, then moves into small blood vessels (capillaries) and is carried away by the bloodstream or reaches the bloodstream through the lymphatic vessels. Protein drugs that are large in size, such as insulin, usually reach the bloodstream through the lymphatic vessels because these drugs move slowly from the tissues into capillaries. The subcutaneous route is used for many protein drugs because such drugs would be digested in the digestive tract if they were taken orally.

Certain drugs (such as progestin, used for birth control) may be given by inserting plastic capsules under the skin (subcutaneously). This route is rarely used.

The intramuscular route is preferred to the subcutaneous route when larger volumes of a drug product are needed. Because the muscles lie below the skin and fatty tissues, a longer needle is used. Drugs are usually injected into muscle in the upper arm, thigh, or buttock. How quickly the drug is absorbed into the bloodstream depends, in part, on the blood supply to the muscle: The sparser the blood supply, the longer the drug takes to be absorbed. The blood supply is increased during physical activity.

For the intravenous route, a needle is inserted directly into a vein. A solution containing the drug may be given in a single dose or by continuous infusion. For infusion, the solution is moved by gravity (from a collapsible plastic bag) or by an infusion pump through thin flexible tubing to a tube (catheter) inserted in a vein, usually in the forearm. Intravenous administration is the best way to deliver a precise dose quickly and in a well-controlled manner throughout the body. It is also used for irritating solutions, which, if given by subcutaneous or intramuscular injection, would cause pain and tissue damage. An intravenous injection can be more difficult to administer than a subcutaneous or intramuscular injection, because inserting a needle or catheter into a vein may be difficult, especially if people are obese.

When given intravenously, a drug is immediately delivered to the bloodstream and tends to take effect more quickly than when given by any other route. Consequently, doctors closely monitor patients who receive an intravenous injection for signs that the drug is working or is causing undesired side effects. Also, the effect of a drug given by this route tends to last for a shorter time.

For the intrathecal route, a needle is inserted between two vertebrae in the lower spine and into the space around the spinal cord. The drug is then injected into the spinal canal. A small amount of local anesthetic is often used to numb the injection site. This route is used when a drug is needed to produce rapid or local effects on the brain, spinal cord, or the layers of tissue covering them (meninges)--for example, to treat infections of these structures. Anesthetics are sometimes given this way.

Sublingual Route: A few drugs are placed under the tongue (taken sublingually) so that they can be absorbed directly into the small blood vessels that lie beneath the tongue. The sublingual route is especially good for nitroglycerin--which is used to relieve angina (chest pain due to an inadequate blood supply to the heart muscle)--because absorption is rapid

and the drug immediately enters the bloodstream without first passing through the intestinal wall and liver. However, most drugs cannot be taken this way because they may be absorbed incompletely or erratically.

Rectal Route: Many drugs that are administered orally can also be administered rectally as a suppository. In this form, a drug is mixed with a waxy substance that dissolves or liquefies after it is inserted into the rectum. Because the rectum's wall is thin and its blood supply rich, the drug is readily absorbed. A suppository is prescribed for people who cannot take a drug orally because they have nausea, cannot swallow, or have restrictions on eating, as is required after many surgical operations. Drugs that are irritating in suppository form may have to be given by injection.

Vaginal Route: Some drugs may be administered vaginally to women as a solution, tablet, cream, gel, or suppository. The drug is slowly absorbed through the vaginal wall. This route is often used to give estrogen to women at menopause, because the drug helps prevent thinning of the vaginal wall, an effect of menopause.

Ocular Route: Drugs used to treat eye disorders (such as glaucoma, conjunctivitis, herpes simplex infection, and injuries) can be mixed with inactive substances to make a liquid, gel, or ointment, so that they can be applied to the eye. Liquid eye drops are relatively easy to use but may run off the eye too quickly to be absorbed well. Gel and ointment formulations keep the drug in contact with the eye surface longer. Solid inserts, which release the drug continuously and in slow amounts, are also available, but they may be hard to put and keep in place. Ocular drugs are almost always used for their local effects. For example, artificial tears are used to relieve dry eyes. Other drugs (for example, those used to treat glaucoma, such as acetazolamide and betaxolol and those used to dilate pupils, such as phenylephrine and tropicamide) produce a local effect after they are absorbed through the cornea and conjunctiva. Some of these drugs then enter the bloodstream and may have unwanted effects on other parts of the body.

Nasal Route: If a drug is to be breathed in and absorbed through the thin mucous membrane that lines the nasal passages, it must be transformed into tiny droplets in air (atomized). Once absorbed, the drug enters the bloodstream. Drugs taken by this route generally work quickly. Some of them irritate the nasal passages. Drugs that can be taken by the nasal route include nicotine (for smoking cessation), calcitonin (for osteoporosis), dihydroergotamine (for migraine headaches), and corticosteroids (for allergies and asthma).

Inhalation: Gases used for general anesthesia, such as nitrous oxide, are given by inhalation. Drugs given by inhalation through the mouth must be atomized into smaller particles than those given by the nasal route, so that the drug can pass through the windpipe (trachea) and into the lungs. How deeply into the lungs they go depends on the size of the droplets; smaller droplets go deeper. Inside the lungs, they are absorbed into the bloodstream. Relatively few drugs are taken this way because inhalation must be carefully monitored to ensure that a person receives the right amount of drug within a specified time. Usually, this method is used to administer drugs that act on the lungs, such as aerosolized antiasthmatic drugs in metered-dose containers.

Cutaneous Route: Drugs applied to the skin are usually used for their local effects and thus are most commonly used to treat superficial skin disorders, such as psoriasis, eczema, skin infections (viral, bacterial, and fungal), itching, and dry skin. The drug is mixed with inactive substances. Depending on the consistency of the inactive substances, the formulation may be an ointment, a cream, a lotion, a solution, a powder, or a gel.

Transdermal Route: Some drugs are delivered bodywide through a patch on the skin. These drugs, sometimes mixed with a chemical (such as alcohol) that enhances penetration of the skin, pass through the skin to the bloodstream without injection. Through a patch, the drug can be delivered slowly and continuously for many hours or days or even

longer. As a result, levels of a drug in the blood can be kept relatively constant. Patches are particular useful for drugs that are quickly eliminated from the body, because such drugs, if taken in other forms, would have to be taken frequently. However, patches may irritate the skin of some people. In addition, patches are limited by how quickly the drug can penetrate the skin. Only drugs to be given in relatively small daily doses can be given through patches. Examples of such drugs include nitroglycerin (for angina), scopolamine (for motion sickness), nicotine (for smoking cessation), clonidine (for high blood pressure), and fentanyl (for pain relief).